**Translation pain research: from animals to patients with chronic pain (including orofacial pain)**

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**Introduction**

Over the last four decades the number of research papers on nociception and pain has increased enormously, leading to impressive advances in the basic knowledge. Studies in animals have been highly successful in providing mechanistic knowledge leading to a better 1) understanding of fundamental pain mechanisms, 2) finding new targets for analgesic compounds, and 3) helping characterisation of clinical signs and symptoms which together has led to a more rational use of available treatments. Although parts of this knowledge have been translated into the benefit of patients, the treatment of chronic pain is still generally unsatisfactory.

Pain studies in patients and volunteers can be addressed mechanistically by experimentally activating different pain pathways and mechanisms.

The concept is that pain can be evoked from different structures (e.g. the orofascial region) using different, quantifiable, and standardized stimulus modalities (thermal, mechanical, chemical, electrical), and the bio-markers can be assessed quantitatively by biochemical, psychophysical, electrophysiological, or imaging methods. Such multi-modal, multi-tissue mechanism-based bio-markers can be used in 1) basic mechanistic studies in healthy volunteers, 2) clinical studies for diagnostic and monitoring purposes and 3) pharmacological studies to profile analgesic potency of new and existing compounds.

Furthermore, the pain system of healthy volunteers can be perturbed and become hypersensitive in order to mimic manifestations seen clinically. The symptoms observed under such conditions may act as a proxy for what is observed clinically (e.g. allodynia, hyperalgesia, hyperpathia) and generate new information about the underlying mechanisms. The development of such human surrogate pain models together with more traditional pain bio-markers have advanced significantly over the last 20 years.

Traditionally the surrogate models have mainly been applied to the skin for obvious reasons but this concept is in these years also undergoing a transition as more and more models are being developed also for other structures like the orofacial region.

**Translational pain bio-markers**

Quantitative pain assessment or quantitative sensory testing (QST) provide psychophysical methods systematically documenting alterations and reorganisation in nervous system function and in particular the nociceptive system. These models have been developed on basis what has been achieved in animal research and therefore to some degree translate from pre-clinical to clinical research. These responses measured in humans can be related to a single stimulus or to a more advanced stimulus paradigm which will activate different mechanisms. Examples of mechanisms which translate from animals to humans are wind-up (temporal summation), diffuse noxious inhibitory control (descending modulation), and receptive fields (reflex receptive fields and referred pain).

Temporal summation can be measured by increased pain response to consecutive stimuli (>0.3Hz) delivered at constant stimulus intensity. Various modalities have been used to induce temporal summation from skin, muscles and viscera, including heat, mechanical pressure, and electricalstimulation.

Descending modulation in humans is assessed by an increase in pain threshold during a tonic experimental pain stimulus. Referred pain is a pain sensation that is perceived at an area other than the site of nociceptive stimulation. The reflex receptive field is a method which reflects the spinal neuronal wiring and how this wiring (e.g. opening latent synapses) may change. Referred pain patterns have been described using experimental stimuli applied to different structures, mostly muscles, joints and viscera.

**Surrogate main models**

The purpose of a human surrogate model is to mimic different aspects of the pain manifestations observed in patients based on sensitisation models in animals. Most of the surrogate models have been transferred from animal studies. As for the pain bio-markers the differentiated approach is important where the attempt is to address different pain conditions with different symptoms, such as neuropathic pain, inflammatory pain, chronic musculoskeletal pain, and chronic visceral pain.

The various models of sensitisation induce different degrees of peripheral and central sensitisation.

#### The clinical symptoms of neuropathic pain e.g. ongoing pain, paraesthesia, dynamic mechanical allodynia, punctate mechanical hyperalgesia, hyperalgesia to cooling, paradoxical heat sensation, sensory loss can be mimicked using different skin models such as burn injury, freeze lesion, UVB irradiation, capsaicin, menthol, electrical stimulation, ischemia, reperfusion and local anaesthetics.

**Conclusion**

Human experimental pain research bridges the gap between basic animal studies and clinical applications and provides better characterisation of pain mechanisms in healthy volunteers and characterise sensory dysfunction in patients with chronic pain, e.g. orofacial pain.

The applications of human quantitative sensory testing are within:

1. the laboratory for basic studies (e.g. peripheral and central hyperexcitability in the trigeminal region) for investigating pain mechanisms
2. the clinic to characterise patients with sensory dysfunctions and/or pain (e.g. TMD pain)
3. the clinic to monitor patients with sensory dysfunctions before and after treatment/surgery (e.g. orthognathic surgery).